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Madison, Wisconsin
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Dr. J. Lein
Bristol Laboratories Inc.
Syracuse, New York

Dear Joe:

I am enclosing a program for a symposium on somatic cell variation that I thought might be of some passing interest to you. The topic, of course, impinges directly on the nature of cancer, but I have to say that nothing very startling came out of this particular meeting. It may be of some ultimate significance in the chemotherapy of cancer that so many tumors do have abnormal chromosome constitutions especially after they have shown some degree of neoplastic progression. This is brought about especially in the contributions by Hauschka and Ford.

The only other item that I wanted to bring up at this time has to do with the microbiological evaluation of potential tumor agents. Certainly the inhibition of growth in an appropriate system would be the simplest basis for an assay, but one might find that this failed for some possible materials. I would like to remind you of an alternative approach which I think may have been brought up before but is more pertinent at the present time. You may have become familiar with Atwood's studies on the effects of iodizing radiations on hetrocariotic conidia of Neurospora. Without going into all of the aspects, one of his useful findings was the efficiency with which segregation of hetrocarions is induced by radiation. In fact, rather small doses are capable of giving measurable increases in the proportion of no longer hetrocariotic spores. I had proposed this some time ago as a method of screening for nucleotoxic agents and, in fact, Charlotte Auerbach has been spending some months with Atwood at Oak Ridge applying similar technics to the screening of various mutagenic chemicals. The procedure is not too complicated to be managed by anyone familiar with the culture of Neurospora. It involves the maintenance of a balanced hetrocarion, preferably with additional colonial or color markers for the hetrocariotic genotype, and then plating treated conidia to examine the fraction which has been made homocariotic by the treatment. In this way the technic is not so much a more sensitive index of inhibition as it is a specific index of nucleotoxic effect as compared to other modes of inhibition, and I would rank a procedure of this kind quite high among possibilities for preliminary screening of agents that might be expected to have antitumor activity. The procedure might also be valuable for the biological assay of a potentially active component.

As a matter of fact, there is a bacterial system which is perhaps theoretically a little bit more obscure but which in practice I am certain will give exactly the same results and which might be rather more easy to handle, especially for weaker agents which ought to be applied over a considerable period of time. This is the induced haploidization of hetrozygous diploids of E. coli and it is described at some length in my 1951 Cold Spring Harbor review. The chief problem here would be the effective maintenance of suitable diploid stocks, but this is not really terribly difficult either, and the whole

technic can rather easily be put on a routine basis. The effect that would be looked for would be the increased proportion of lac minus, haploid, segregates out of treated cultures of a balanced hetrozygote. One advantage of the bacterial system is its extreme sensitivity and we were able to diagnose genetic effects of doses of radiations and chemicals that had quite small bactericidal effects in total. Again, I would recommend this type of procedure for the biological assay only if a simpler growth inhibition were not readily available for a particularly promising compound. On the other hand, I would think that this assay approach should be quite valuable in the primary screening of nucleotoxic compounds such as might arise in the attempts at substitutional chemotherapy, and in fact it might be applied quite independently of growth inhibitory effects if the latter happened to be not too powerful. If your reading of the Cold Spring Harbor account, between pages 428 and 430 and referring to figures 7A and 7B, suggest that we ought to go further into this, I will give you a more detailed prescription on how you might go after it.

It is quite unlikely now that I will be going down to the meetings, but if you can find time for a side trip to Madison from Chicago, we'll be very glad to see you here. Esther may show up on the 29th.

With all best regards.

Your sincerely,

Joshua Lederberg

JL:ac

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copy sent to Dr. Lederberg 5/8/58